CAPTOPRIL IN CONGESTIVE HEART FAILURE

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1 Vasodilator therapy is used widely for the treatment of congestive heart failure irrespective of its origin. The acute and long-term effects of captopril were studied in 50 patients with congestive heart failure due to valvular incompetence, hypertension, cardiomyopathy, and ischaemic heart disease. Haemodynamic studies were performed in all patients. In those with valvular incompetence, regurgitation fractions were measured cineangiographically. In patients with ischaemic heart disease coronary sinus blood flow was assessed by a thermodilution technique. During clinical follow-up patients were studied by non-invasive techniques including electrocardiography, echocardiography and chest radiography.

2 In the short-term studies, left ventricular filling pressure, total peripheral resistance, and end-diastolic and end-systolic volumes decreased after captopril, while cardiac output, stroke volume, and ejection fraction increased. Valvular regurgitation fraction was assessed in 10 patients with aortic or mitral insufficiency. In every patient the regurgitation fraction decreased. Coronary blood flow was measured in eight patients with severe ischaemic heart disease. In three patients it remained constant and in the other five patients it decreased. At the same time a highly significant decrease of myocardial oxygen consumption was measured.

3 During long-term treatment clinical improvement occurred in most of the patients. This was documented by a reduction of ventricular diameters in hypertensive heart disease as well as in valvular incompetence. These values remained constant in congestive cardiomyopathy despite clinical improvement. Serious hypotensive episodes were observed in eight patients with valvular stenosis or complex congenital cardiac abnormalities.

4 Captopril is therefore an effective vasodilator for the treatment of congestive heart failure. In patients with intact left ventricular function captopril should not be given because severe hypotensive episodes may occur. Ischaemic heart disease with congestive heart failure is no contraindication for treatment with captopril because the reduction in myocardial blood flow is balanced by the reduced myocardial oxygen consumption.

Introduction

Vasodilators are effective in treating congestive heart failure because they reduce the increased preload and afterload in such patients (Cohn 1981). Since the renin-angiotensin system plays an important part in the development of vasoconstriction and fluid retention in congestive heart failure, blockade of this system may help to reverse congestion and increased afterload in congestive heart failure. Numerous studies have reported a beneficial effect of captopril in congestive heart failure (Liebau, 1982). Acute administration of the drug to these patients results in a considerable reduction of blood pressure, total peripheral resistance, and pulmonary pressure, while cardiac output increases (Liebau *et al.*, 1981). These effects are maintained during long-term treatment (Liebau *et al.*, 1981).

Vasodilator treatment may, however, be hazardous in some of these patients. A high preload may be needed to maintain a sufficient stroke volume, according to the Starling curve, and dramatic reduction of blood pressure might result in underperfusion of vital organs, especially of the heart and the brain, while increased cardiac output might result in excess perfusion of less vital organs such as the skin or intestine.

The purpose of the present study was to define further criteria for vasodilator treatment in congestive heart failure according to its aetiology and haemodynamic effects and to identify subgroups of patients who are likely to benefit from captopril and those who are likely to worsen during captopril treatment.

Methods

Since 1979 a total of 50 patients with congestive heart failure have been treated with captopril and studied at regular intervals from 14 to 42 days for up to 30 months. New York Heart Association classification, electrocardiography and chest radiography were performed regularly by standard techniques. In 10 patients acute haemodynamic effects were measured during diagnostic cardiac catheterisation (right-heart catheterisation with a Swan-Ganz thermodilution catheter, left heart catheterisation with an F7 pigtail catheter for pressure measurement, and left ventricular angiogram (40° RAO, Conray 40 ml, 20 ml/sec)). These manoeuvres were performed before and 60 minutes after a single oral dose of 50 mg captopril. Left ventricular volume and ejection fraction were calculated using the area-length method. Valvular regurgitation fraction was calculated from the difference between the angiographically obtained stroke volume and that obtained from thermodilution.

Coronary sinus flow was measured in eight patients before and 60 minutes after a single dose of 50 mg captopril. For this purpose, a coronary sinus thermodilution catheter was placed with the tip in the vena cordis magna. Left ventricular myocardial blood flow was measured by continuous infusion of saline at room temperature. Myocardial oxygen consumption was calculated from the atrioventricular difference of oxygen saturations.

Patients were divided into three groups according to the diagnosis: group 1—patients with congestive cardiomyopathy; group 2—patients with aortic insufficiency, mitral insufficiency, and combined aortic and mitral disorders; and group 3—patients with coronary heart disease and hypertensive heart disease.

Results

Long-term treatment

Fifty patients were studied over 3 to 30 months. In addition to captopril, all patients were simultaneously taking digitalis and diuretics. In 12 patients captopril treatment had to be discontinued because of side effects: ageusia in two, hypotension in three, and eosinophilia in two. All patients who developed severe hypotension had normal left ventricular size. The aetiology of coronary heart disease is presented in Table 1. Ten patients died during the observation period but none of the deaths was directly associated with captopril (Table 2).

New York Heart Association classification, left ventricular diameter, and cardiothoracic ratio changed in most of the patients during captopril

Table 1 Diagnosis of patients who suffered severe hypotensive episodes after captopril

Mitral stenosis	2 cases
Primary pulmonary hypertension	2 cases
Tetralogy of Fallot	1 case
Single ventricle	1 case
Ischaemic heart disease	1 case
Pericarditis	1 case

treatment, with striking differences according to the cause of congestive heart failure (groups 1, 2 and 3, Table 3).

Group 1: Most of the patients with congestive cardiomyopathy showed some clinical improvement (Figure 1). Left ventricular end-diastolic diameter and cardiothoracic ratio were, however, unchanged in most patients during the course of the treatment (Figures 2, 3).

Group 2: There was a significant reduction in end-diastolic left ventricular diameter and cardiothoracic ratio. These patients also showed significant clinical improvement (Figures 1–3).

Group 3: The overall results in coronary heart disease and hypertensive patients are shown in Figures 1–3. The improvement of the clinical state was less pronounced than in group 2 but greater than in group 1. The same was true for cardiothoracic ratio and ventricular diameters. The diverse results are due to the heterogeneity of the underlying heart diseases represented in this group.

Invasive studies

In most patients myocardial blood flow decreased with the fall in blood pressure after captopril intake, but none of the patients suffered angina. Myocardial oxygen consumption also decreased considerably (Figures 4, 5).

Left ventricular volumes were smaller 60 minutes after captopril ingestion in the patients with aortic or mitral valve incompetence. This effect, together with the sharp reduction in blood pressure, lowered regurgitation fraction significantly. The haemodynamic changes which followed administration of captopril are summarised in Table 4 and Figures 6 and 7.

Discussion

Vasodilator therapy has been shown to be very effective in the treatment of congestive heart failure. Nevertheless, some patients do not benefit from this treatment. In some of these, there is very little or no

Table 2 Causes of death occurring during captopril therapy

Case no	Sex	Age	Diagnosis	Cause
1	M	74	Congestive cardiomyopathy	Cerebral
2	F	70	Mitral stenosis	Cardiac
3	F	50	Mitral stenosis	Cerebral
4	F	70	Myocardial infarction	Cerebral
5	M	46	Aortic insufficiency, aortic stenosis	Perioperatively
6	M	69	Myocardial infarction, aneurysm	Vascular
7	M	40	Congestive cardiomyopathy	Cardiac
8	M	45	Congestive cardiomyopathy	Cardiac
9	M	65	Mitral stenosis	Cardiac
10	M	35	Single ventricle	Cardiac
11	M	60	Pericarditis	Cardiac

Table 3 New York Heart Association classification, left ventricular end-diastolic diameter, cardiothoracic ratio, and duration of treatment (mean $\pm$ SEM) before and during treatment with captopril.

	Group 1		Group 2		Group 3	
	Baseline	Captopril	Baseline	Captopril	Baseline	Captopril
New York Heart Association class	3.5 ± 0.2	3.0 ± 0.3	3.3 ± 0.3	1.5** ± 0.1	2.9 ± 0.2	1.8* ± 0.2
Left ventricular end-diastolic dimension (mm)	66 ± 4	68 ± 3	65 ± 4	58* ± 3	59 ± 3	55 ± 1
Cardiothoracic ratio	0.54 ± 0.02	0.54 ± 0.02	0.54 ± 0.02	0.51 ± 0.02	0.52 ± 0.02	0.51 ± 0.01
Months on therapy		11 ± 2		11 ± 2		14 ± 3

* $p < 0.05$, ** $p < 0.01$ **Figure 1** Individual changes of New York Heart Association classes during captopril treatment in patients with congestive heart failure.

Figure 2 Individual changes of left ventricular end-diastolic dimension during captopril treatment in patients with congestive heart failure.

Figure 3 Individual changes in cardiothoracic ratio during captopril treatment in patients with congestive heart failure.

Figure 4 Left ventricular volumes before and 60 minutes after oral intake of 50 mg captopril in patients with valvular incompetence.

Figure 5 Stroke volume index and regurgitation volume index before and 60 minutes after oral intake of 50 mg captopril in patients with valvular incompetence.

Table 4 Haemodynamic parameters (mean $\pm$ SEM) before and 60 minutes after 50 mg captopril in 10 patients.

		Before captopril	60 minutes after captopril
Systolic blood pressure	(mm Hg)	150.5 $\pm$ 12.9	119.1 $\pm$ 10.6**
Diastolic blood pressure	(mm Hg)	68.5 $\pm$ 5.2	49.5 $\pm$ 8.5**
Cardiac index	(l/min m ²)	2.8 $\pm$ 0.2	3.0 $\pm$ 0.2
Regurgitation fraction	(%)	54.0 $\pm$ 4.9	34.4 $\pm$ 6.5**
End-diastolic volume index	(ml/m ²)	138.7 $\pm$ 26.4	103.4 $\pm$ 11.7**
End-systolic volume index	(ml/m ²)	76.9 $\pm$ 15.5	48.2 $\pm$ 8.9*
Left ventricular end-diastolic pressure	(mm Hg)	17.2 $\pm$ 2.7	9.7 $\pm$ 1.7**
Pulmonary artery pressure	(mm Hg)	26.1 $\pm$ 4.9	17.3 $\pm$ 4.4*
Heart rate	(l/min)	78.0 $\pm$ 3.7	72.8 $\pm$ 8.3

* $p < 0.05$, ** $p < 0.01$

clinical improvement, whereas in others the effects are limited to acute haemodynamic improvement and long-term treatment is ineffective (Colucci *et al.*, 1981). Furthermore, severe hypotensive episodes may develop, especially at the beginning of vasodilator therapy.

Our data have shown that effectiveness of vasodilator treatment depends on the underlying heart disease. In patients with valvular heart disease captopril acts by reducing afterload, which increases cardiac output. The reduction in systolic pressure gradient at the mitral valve and diastolic pressure gradient at the aortic valve results in a significant

Figure 6 Left ventricular myocardial blood flow before and 60 minutes after oral intake of 50 mg captopril. **Figure 7** Myocardial oxygen consumption before and 60 minutes after oral intake of 50 mg captopril.

decrease in regurgitation volume. Furthermore, there is a considerable reduction in end-diastolic ventricular volume, which also reduces valvular area and therefore regurgitation volume. For these reasons vasodilator therapy may be curative provided there is no progression of valvular disease per se. Hence, congestive heart failure in these patients is primarily due to an increased load on the ventricular volume by the load produced by regurgitation volume, which is reversed by captopril. In some of our patients valvular replacement could be delayed for more than 2 years. Prophylactic vasodilation might in fact be a reasonable treatment in patients with valvular heart disease without congestive heart failure (Hockings *et al.*, 1980; Greenberg *et al.*, 1982).

In patients with congestive cardiomyopathy these effects of captopril are less pronounced. Despite clinical improvement, no significant reduction of ventricular volume or end-diastolic ventricular diameters can be shown. This might be due to morphological changes of the myocardium in these patients, resulting in a stiffer ventricular wall than in patients with valvular disease. Furthermore, vasodilator therapy counteracts only the symptoms of congestive heart failure in patients with congestive cardiomyopathy: the underlying disease is not affected. For this reason, captopril may prolong survival of these patients by reversing vasoconstriction but progression of congestive cardiomyopathy induced by deterioration of cardiac structure remains unchanged.

In congestive heart failure induced by coronary heart disease blood pressure reduction may be dangerous because it reduces myocardial perfusion, and if this induced myocardial ischaemia angina would occur. Despite pronounced reduction of myocardial blood flow, none of the patients with coronary heart disease developed such symptoms. This phenomenon may probably be explained by the

reduction of myocardial oxygen consumption owing to reduced preload and afterload (Ford, 1980; Ikram *et al.*, 1981). Since the decrease in myocardial blood flow parallels the decrease in systemic blood pressure, direct vasodilatation of coronary arteries is not induced by converting-enzyme blockade. Therefore the occurrence of steal effects may be excluded. For this reason captopril may be used for the treatment of hypertension and congestive heart failure in patients with coronary heart disease without any special limitations.

Captopril may produce severe hypotensive episodes in hypertensive patients if hypovolaemia is induced by diuretics before administration of captopril. In our series we observed similar episodes in patients with congestive heart failure after captopril. All of these patients presented unique findings: the left ventricular myocardial function was intact but a high left atrial pressure was needed to supply a sufficient volume load to the left ventricle. An exact diagnosis of the underlying heart disease should therefore precede the prescription of vasodilators in congestive heart failure.

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